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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/766,273	BITTNER ET AL.	
	Examiner	Art Unit	
	Robert T. Crow	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29,31,32,34,36 and 38-44* is/are pending in the application.

4a) Of the above claim(s) *39-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29,31,32,34,36,38 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 4 June 2007 in which claims 1, 34, 36, and 38 were amended, claims 30, 33, 35, and 37 were canceled, and no new claims were added. All of the amendments have been thoroughly reviewed and entered.

The interview summary is acknowledged and the interview record is complete.

The objections to the claims listed in the previous Office Action are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 112, second paragraph, are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

Claims 1-29, 31-32, 34, 36, 38, and 44 are under prosecution.

Noncompliant Amendment

2. It is noted that the Remarks filed 4 June 2007 has several errors therein. Specifically, Applicant's arguments in Section VIII on page 14 of the Remarks refer to the previous rejection of "claims 1 and 18" as obvious over Mirkin et al in view of Klinger et al. However, the previous rejection over Mirkin et al in view of Klinger et al concerned claim 20, not claim 18. Claim 18 was previously rejected as obvious over Mirkin et al.

For the purposes of examination and in the interest of customer service and compact prosecution, Applicant's arguments regarding the rejection of claim 1-5, 14-15, 17, 19, 24-25, 28, 30-32 and 44 as anticipated by Mirkin et al under 35 USC 102(b) are accordingly applied to the rejection of claim 18 as obvious over Mirkin et al, because the both the previous 102(b) rejections and the 103(a) rejection of claim

18 are based on the same reference. Thus, any deficiencies of Mirkin et al regarding anticipation of a claim are accordingly applied to the obviousness rejection of any claim over Mirkin et al as the sole reference.

Because the arguments in Section VIII on page 14 of the Remarks refer to the teachings of Mirkin et al in view of Klinger et al, Section VIII is accordingly considered a response to the rejection of claim 20 as obvious over Mirkin et al in view of Klinger et al.

3. Further, Applicant's arguments in Section X on pages 14-15 of the Remarks are directed to the previous rejection claims "1, 23, and 27" as obvious over Mirkin et al in view of Bruchez et al. However, Applicant has not included claim 26, which was also rejected over the cited prior art, in this section of the Remarks. This appears to by a typographical omission, because claim 27 is dependent upon claim 26.

Because of the dependency of claim 27 on claim 26, any arguments regarding claim 27 must necessarily include claim 26. Therefore, for the purposes of examination and in the interest of customer service and compact prosecution, Section X on pages 14-15 of the Remarks is accordingly considered a response to the rejection of claims 1, 23, and 26-27.

4. It is also noted that Applicant's two previous responses, filed 6 November 2006 and 20 February 2007, were also non-compliant. Applicant has thus failed to correct all of the errors indicated in the Notices of Non-Compliant Amendment mailed 19 January 2007 and 3 may 2007. It is emphasized that Applicant's response filed 4 June 2007 has been considered in the interest of customer service and compact prosecution to prevent any further delay in prosecution. However, for the response to this Office Action to be complete, Applicant is **REQUIRED** to correct the errors listed above and file amendments that are compliant with 37 CFR 1.121. Failure to comply with this requirement will be considered **nonresponsive** and will **not** be considered a bona fide attempt to respond.

5. The following rejections are new rejections necessitated by the amendments.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-5, 14-15, 17-19, 23-28, 31-32, 34, 36, 38, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) and further in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999).

It is noted that a prior art reference is considered as a whole and for all it stands for. Thus, while the rejections listed below present a modified interpretation of the teachings of Mirkin et al in view of Pinkel et al solely for the purpose of clarity, the rejections of the claims are maintained for the reasons of record. While Applicant has amended the claims, the amendments do not affect the claimed invention. Thus, the claims are still obvious over Mirkin et al in view of Pinkel et al as discussed below.

Regarding claim 1, 23, and 26-27, Mirkin et al teach a method for assaying a first sample for a first probe. In a single exemplary embodiment, Mirkin et al teach providing a substrate attached to a first target; namely, a substrate comprising a plurality of initial type of oligonucleotides attached to the substrate in an array of spots, wherein each spot contains a different type of oligonucleotide (page 40, line 30-page 41, line 11). The plurality of different initial type of oligonucleotides attached in an array of spots is the claimed plurality of different targets attached to a substrate. Because there are different types of targets, each target can preferentially bind to a corresponding different probe polynucleotide. The substrate is contacted with the first sample, wherein the first sample is suspected of comprising the first probe; namely, analyte DNA is added to the substrate (Figure 13B); the instantly claimed "first probe" is the analyte DNA of Figure 13B, and the instantly claimed "targets" are the adsorbed thiol modified DNA of Figure 13B. The first probe comprises a first probe polynucleotide comprising a first tag sequence which does not bind to the first target and a first binding sequence which does bind to the first target, and wherein contacting the substrate with the first sample takes place under conditions in which the first binding sequence can bind to the first target; namely, Figure 13B shows part of the first probe hybridizing to the immobilized targets through a first binding sequence, and the remainder of the first probe is a first tag sequence available to bind to DNA modified nanoparticles. The DNA modified nanoparticles of Figure 13B are the tag-binding conjugate, which binds to the first tag sequence. The nanoparticles are a semiconductor nanoparticles (page 19, lines 24-34), and determining if the semiconductor nanocrystal is associated with the substrate occurs because Mirkin et al teach color changes resulting from binding on the substrate are noted (page 83, lines 18-20 and Figure 13B, last step).

While Mirkin et al also teach a plurality of different targets attached to the substrate and each of the different targets preferentially binds a different probe polynucleotide (e.g., a plurality of oligonucleotides are provided in an array to detect multiple different nucleic acids; page 40, line 32-page 41, line 11), Mirkin et al does not teach separate determination of each binding event.

However, Pinkel et al teach a method of assaying samples for probes by using a biosensor array to detect nucleic acid binding complexes (Abstract), wherein each binding event is separately determined; namely, simultaneous assaying of binding components of a test sample are done on by discretely detection at individual locations (i.e., bundles of fibers; Abstract) with the added benefit that the discrete addressing assists in rapid sample identification (Abstract). Thus, Pinkel et al teach the known technique of separately determining each binding event on an array.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the detection of multiple different binding events as taught by Mirkin et al with separately determined detection as taught by Pinkel et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in rapid sample identification as explicitly taught by Pinkel et al (Abstract). In addition, it would have been obvious to the ordinary artisan that the known technique of using the separate determination of each binding event on an array of Pinkel et al could have been applied to the method of Mirkin et al with predictable results because the separate determination of Pinkel et al predictably results in detection of all of the binding events during a microarray hybridization assay.

Neither Mirkin et al nor Pinkel et al teach each conjugate comprises different semiconductor nanocrystals with different fluorescence characteristics (i.e., claim 1 and 23) or shells (i.e., claims 26-27).

However, Weiss et al teach the use of semiconductor nanocrystals attached to probes (i.e., affinity molecules) to determine the presence of a detectable substance in a material (Abstract), wherein the probes (i.e., affinity molecules) are nucleic acids (column 6, lines 50-67) and wherein a plurality of differently colored semiconductor probes each having different semiconductor nanocrystals are used by shining light on the crystal and detecting the fluorescence (i.e., claim 23; column 1, lines 50-65). The nanocrystals encompass shell particles of CdS (i.e., claims 26-27; column 6, lines 17-35). Weiss et al also teach the particles have the added benefit of allowing detection of a plurality of detectable substances

without overlap of the signals (column 6, lines 35-47). Thus, Weiss et al teach the known technique of using different semiconductor nanocrystals in each probe (i.e., claim 1), wherein the nanocrystals are excited and fluoresce (i.e., claim 23), and have CdS shells (i.e., claims 26-27).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of semiconductor nanocrystals as taught by Mirkin et al and Pinkel et al with different nanocrystals as taught by Weiss et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing simultaneous detection of a plurality of detectable substances without overlap as explicitly taught by Weiss et al (column 6, lines 35-47). In addition, it would have been obvious to the ordinary artisan that the known technique of using the different nanocrystals as taught by Weiss et al could have been applied to the method of Mirkin et al in view of Pinkel et al with predictable results because the different nanocrystals as taught by Weiss et al predictably result in detection of binding events during a microarray hybridization assay.

Regarding claim 2, the method of claim 1 is discussed above. Mirkin et al also teach the substrate is a slide (page 82, lines 30-34).

Regarding claim 3, the method of claim 1 is discussed above. Mirkin et al further teach the substrate comprises a plurality of different targets; namely, the substrate has rows of spots, each spot containing a different type of oligonucleotide (page 41, lines 2-11).

Regarding claim 4, the method of claim 3 is discussed above. Mirkin et al teach the substrate comprises a microarray (page 40, lines 32-35).

Regarding claim 5, the method of claim 1 is discussed above. Mirkin et al also teach the first probe polynucleotide is produced from an amplification process comprising a polymerase chain reaction; namely, the nucleic acid being detected is in a polymerase chain reaction (i.e., PCR) solution (page 24, lines 18-24).

Regarding claims 14 and 15, the method of claim 1 is discussed above. Mirkin et al further teach the first tag sequence is located at or nearer either the 5′ end (i.e., claim 14) or the 3′ end (i.e., claim 15) of the first probe polynucleotide; namely, oligonucleotides are functionalized for attachment to solid surfaces at either their 3′ termini or their 5′ termini (page 21, line 34-page 22, line 22). The end that is attached dictates which end is the overhang of the linking oligonucleotide (i.e., the first tag sequence) will be on; i.e., if the first target is attached to the slide on its 3′ end, he first tag sequence will be on the 3′ end of the probe. Because Mirkin et al teach attachment of the first target to the substrate at either end, and because the attachment end of the first target dictates which end the first tag is located on, Mirkin et al anticipate the location of the tag sequence at either end of the first probe polynucleotide.

Regarding claim 17, the method of claim 1 is discussed above. Mirkin et al teach contacting the sample with the first target takes place prior to contacting the sample with the first tag-binding conjugate (Example 10).

Regarding claim 18, the method of claim 1 is discussed above. With respect to contacting the sample with the first target after contacting the sample with the first tag-binding conjugate, the courts have held that selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results (*In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946). See MPEP 2144.04 IV.C. Because Mirkin et al teach all of the steps required in claim 18, the claim is obvious over Mirkin et al in view of Pinkel et al and Weiss et al.

Regarding claim 19, the method of claim 1 is discussed above. Mirkin et al also teach contacting the sample with the first target takes place simultaneously contacting the sample with the first tag-binding conjugate (Example 10). It is noted that during the final step of hybridization step of Example 10 (page 83, lines 10-20), both the sample (i.e., the linking oligonucleotide) and the first tag-binding conjugate (i.e., the complementary oligonucleotide attached to the semiconductor nanoparticle) are both present; therefore, the contacting of the sample with the first target and the first tag-binding conjugate is occurring simultaneously.

Regarding claims 24 and 25, the method of claim 1 is discussed above. Mirkin et al further teach the first semiconductor nanocrystal comprises a core of CdSe (page 19, lines 24-26).

Regarding claim 28, the method of claim 1 is discussed above. Mirkin et al teach the sample is assayed to determine if the probe is present in the sample; namely, the method detects hybridized nucleic acids (Abstract).

Regarding claim 31, the method of claim 1 is discussed above. Mirkin et al also teach the substrate is washed, by rinsing with buffer, prior to determining of the first semiconductor nanocrystal is associated with the first target (page 83, lines 10-20).

Regarding claim 32, the method of claim 1 is discussed above. Mirkin et al further teach a medium is added to the substrate to dilute the concentration of the first semiconductor nanocrystal prior to determining of the semiconductor nanocrystal is associated with the first target; namely, the substrate is removed and rinsed with a buffer (page 83, lines 10-20). Thus, after removal, the nanoparticles are at a concentration on the substrate, and the rinsing of the substrate, by introducing more fluid (but not more nanoparticles) to the substrate, thereby diluting the nanoparticles.

Regarding claim 34, the method of claim 33 is discussed above. Pinkel et al also teach the binding of each different probe polynucleotide to its corresponding different target can be separately determined through a different identified position at which each different target is attached to the substrate; namely, the substrate comprises fibers to which the nucleic acids (i.e., binding partners) are attached, and each fiber is uniquely identified and discretely addressed to detectors, which has the added advantage of allowing transmission of unique pattern to assist in rapid identification of the sample in the sensor (Abstract). Thus, Pinkel et al teach the known technique of using different identified positions.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Mirkin et al in view of Pinkel et al and Weiss et al with the different identified positions of Pinkel et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said

modification would have resulted in a method having the added advantage of allowing transmission of unique pattern to assist in rapid identification of the sample in the sensor as explicitly taught by Pinkel et al (Abstract). In addition, it would have been obvious to the ordinary artisan that the known technique of using the different identified positions of Pinkel et al could have been applied to the method of Mirkin et al in view of Pinkel et al and Weiss et al with predictable results because the different identified positions of Pinkel et al predictably results in high quality data from hybridization assays.

Regarding claim 36, the method of claim 33 is discussed above. Pinkel et al also teach the hybridization of each different probe polynucleotide to its corresponding different target can be separately determined by the conditions under which it hybridizes; namely, hybridization occurs under defined stringency conditions, which has the added advantage of allowing control of the amount mismatch sequences hybridized (column 6, lines 16-30), which prevents false positive from being created in an assay. Thus, Pinkel et al teach the known technique of using separate determination conditions.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Mirkin et al in view of Pinkel et al and Weiss et al with the separate determination conditions of Pinkel et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of preventing false positive from being created in an assay as a result of controlling the amount of mismatch hybrids as explicitly taught by Pinkel et al (column 6, lines 16-30). In addition, it would have been obvious to the ordinary artisan that the known technique of using the separate determination conditions of Pinkel et al could have been applied to the method of Mirkin et al in view of Pinkel et al and Weiss et al with predictable results because the separate determination conditions of Pinkel et al predictably results in high quality data from hybridization assays.

Regarding claim 38, the method of claim 33 is discussed above. Mirkin et al also teach the method wherein each different probe polynucleotide is bound to a different tag-binding conjugate which

comprises a different semiconductor nanocrystal; namely, each spot in the array is assayed with oligonucleotide nanoparticle conjugates (page 41, lines 1-11), wherein the nanoparticle is a semiconductor nanoparticle (page 19, lines 24-34), and wherein the oligonucleotide nanoparticle conjugates are attached to the same type of particle (Example 10 and Figure 13B). The broad limitation "a different semiconductor nanocrystal" is interpreted in the instant claim to mean the tag-binding conjugates are each bound to a different (i.e., physically distinct) particle (e.g., Figure 13B).

Regarding claim 44, the method of claim 1 is discussed above. Mirkin et al also teach the target is a polynucleotide is located in a cell, which may be fixed or unfixed (page 24, lines 18-20).

Response to Arguments

Applicant's arguments filed 4 June 2007 (i.e., the "Remarks") have been fully considered but they are not persuasive for the reason(s) listed below.

It is noted that the amendments to the claims have included the limitations of previous claims limitations of the previous version of claim 33 and 35 into claim 1; thus, Applicant's arguments on pages 16-17 of the Remarks will be addressed first.

A. Applicant argues on pages 16-17 of the Remarks that when fluorescent dyes are described n Mirkin, there is a donor-acceptor motif that quenches the dye upon hybridization to the sequence.

However, this argument is irrelevant because neither the claims nor the rejections require or detail the use of the donor-acceptor function or fluorescent dyes. Thus, Applicant's argument is irrelevant.

B. Applicant also argues on pages 16-17 of the Remarks that Mirkin et al does not describe the use of varying nanoparticles and tag sequences in Figure 13 because it is contrary to the primary objective of amplifying the signal of Mirkin.

However, Applicant states in the first full paragraph on page 17 of the Remarks that the detectable change of Mirkin et al is detected upon hybridization of the nanoparticle linked tags to the immobilized target nucleotide sequences, and that the sequences provide a facet for signal amplification. Thus, Applicant admits the particles are used in nucleic acid hybridization events and that the detection is based on hybridization of nanoparticles having tag binding conjugates. Figure 13B, as detailed in the rejections presented above, shows the claimed arrangement of an immobilized target, a probe with tag and binding sequences, and a hybridized nanoparticle-labeled tag-binding conjugate. Thus, Figure 13B describes (on pages 40-41 of Mirkin et al) detection of a target using the probes and tag binding conjugate.

Mirkin et al also teach the detection of multiple different targets using spotted arrays in the first paragraph on page 41 wherein "the rest of the assay is performed in one of the ways described above," which includes Figure 13B. Thus, multiplex detection on an array is taught by Mirkin et al because Figure 13B is interpreted as a representation of **a single spot** in the array of different spots of Mirkin et al. One spot having a specific target is detected as the darkened area, and other spots having different targets are also detected as other darkened areas if a hybridization event occurs at those particular target spots. Thus, specific tag sequences having nanoparticles are bound to specific target in the array. All other dendrimer components are encompassed by the open claim language "comprising" of the instant claims.

C. In response to applicant's arguments on page 17 of the Remarks against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Specifically, while Mirkin et al teach the detection of multiple different targets, Pinkel et al is relied upon for the "separately determined" detection, and Weiss et al is relied upon for the teaching of a different nanoparticle on each tag binding conjugate.

D. In response to applicant's argument on page 17 of the Remarks that there is no suggestion to combine the references, while the examiner recognizes that obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, such a suggestion does not have to be in the reference, but can be in the general knowledge of a person or ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the ordinary artisan would have been motivated to make the modification of Pinkel et al because said modification would have resulted in a method having the added advantage of preventing false positive from being created in an assay as a result of controlling the amount of mismatch hybrids as explicitly taught by Pinkel et al (column 6, lines 16-30). Further, the ordinary artisan would have been motivated to make the modification of Weiss et al because the modification has the added benefit of allowing detection of a plurality of detectable substances without overlap of the signals (column 6, lines 35-47).

In addition, it is also noted that under the Supreme Court ruling for *KSR Int'l Co. v. Teleflex, Inc* (No 04-1350 (US 30 April 2007) forecloses the argument that a **specific** teaching suggestion, or motivation is required to support a finding of obviousness. See *Ex parte Smith* (USPQ2d, slip op. at 20 (Bd. Pat. App. & Interf. June 25, 2007).

E. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

F. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., multiplexing) are not actually recited in the rejected claim(s) because the term "multiplexing" is not used in the claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

G. As noted above in Section 2, Applicant's arguments in Section VIII on page 14 of the Remarks refer to the previous rejection of "claims 1 and 18" as obvious over Mirkin et al in view of Klinger et al. However, the previous rejection over Mirkin et al in view of Klinger et al concerned claim 20, not claim 18. Claim 18 was previously rejected as obvious over Mirkin et al.

For the purposes of examination and in the interest of customer service and compact prosecution, Applicant's arguments regarding the rejection of claim 1-5, 14-15, 17, 19, 24-25, 28, 30-32 and 44 as anticipated by Mirkin et al under 35 USC 102(b) are accordingly applied to the rejection of claim 18 as obvious over Mirkin et al, because the both the previous 102(b) rejections and the 103(a) rejection of claim 18 are based on the same reference. Thus, any deficiencies of Mirkin et al regarding anticipation of a claim are applicable to the obviousness rejection of any claim over Mirkin et al as the sole reference. However, the previous rejection over Mirkin et al in view of Klinger et al concerned claim 20, not claim 18. Claim 18 was previously rejected as obvious over Mirkin et al.

Because the arguments in Section VIII on page 14 of the Remarks refer to the teachings of Mirkin et al in view of Klinger et al, Section VIII is accordingly considered a response to the rejection of claim 20 as obvious over Mirkin et al in view of Klinger et al.

Further, Applicant's arguments with respect to the previous rejections of claims 20 and 18 rely on arguments regarding the alleged deficiencies of Mirkin et al. These arguments are addressed above as they apply to the new rejections necessitated by the amendments. Since the arguments regarding the teachings of Mirkin et al in view of Pinkel et al and Weiss et al were not persuasive, the remaining rejections of the claims are maintained.

H. As also noted above in Section 3, Applicant's arguments in Section X on pages 14-15 of the Remarks are directed to the previous rejection claims "1, 23, and 27" as obvious over Mirkin et al in view of Bruchez et al. However, Applicant has not included claim 26, which was also rejected over the cited prior art, in this section of the Remarks. This appears to by a typographical omission, because claim 27 is dependent upon claim 26; thus, any arguments regarding claim 27 must necessarily include claim 26. Because of the dependency of claim 27 on claim 26, any arguments regarding claim 27 must necessarily include claim 26. Therefore, for the purposes of examination and in the interest of customer service and compact prosecution, Section X on pages 14-15 of the Remarks is accordingly considered a response to the rejection of claims 1, 23, and 26-27.

Further, Applicant's arguments with respect to claims 1, 23, and 26-27 have been considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

I. Applicant's remaining arguments regarding the dependent claims rely on arguments regarding the alleged deficiencies of Mirkin et al. These arguments are addressed above as they apply to the new rejections necessitated by the amendments. Since the arguments regarding the teachings of Mirkin et al in view of Pinkel et al and Weiss et al were not persuasive, the remaining rejections of the claims are maintained.

9. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) and further in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) as applied to claim 1 above, and further in view of Pearson et al (U.S. Patent No. 5,916,779, issued 29 June 1999).

Regarding claim 6, the method of claim 1 is discussed above in Section 8.

While Mirkin et al teach amplification of the probe polynucleotide (page 24, lines 32-34), Mirkin et al, Pinkel et al, and Weiss et al are silent with respect to reverse transcriptase.

However, Pearson et al teach a method of amplifying polynucleotides by contacting the sample with reverse transcriptase under conditions that reverse transcribe RNA to DNA (Abstract) with the added benefit that amplification of RNA targets is useful for monitoring upregulation of cancer genes (column 2, lines 13-25).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising amplification as taught by Mirkin et al in view of Pinkel et al and Weiss et al with amplification using reverser transcriptase as taught by Pearson et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in amplification of RNA targets useful for monitoring upregulation of cancer genes as explicitly taught by Pearson et al (column 2, lines 13-25).

10. Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) and further in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) as applied to claim 1 above, and further in view of Fischer (U.S. Patent No. 5,876,932, issued 2 March 1999).

Regarding claims 7-9, the method of claim 1 is discussed above in Section 8.

While Mirkin et al teach amplification of the probe polynucleotide (page 24, lines 32-34), Mirkin et al, Pinkel et al, and Weiss et al are silent with respect to primers.

However, Fischer teaches a method for assaying a sample for a probe in the form of assaying for gene expression (Abstract) comprising incorporating the first tag sequence into the first probe polynucleotide by employing a first primer polynucleotide; namely, the sequence being detected is amplified (i.e., claim 7; Figure 1). Fischer also teaches claim 8, wherein the primer binds the polyadenlyated tail of mRNA (e.g., Figure 1, step 1; Figure 2, step 2; and column 4, lines 64-67), as well as

claim 9, wherein the primer binds to a plurality of different sequences because degenerate random primers are used; column 3, lines 25-39).

The support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed is discussed above. Because Fischer teaches producing the first probe polynucleotide through amplification employing a first primer (Figure 1), and because the first probe polynucleotide must contain the tag sequence as required by claim 1, the first primer must incorporate the tag sequence into to first probe polynucleotide (otherwise, the first primer would not direct the synthesis of the first probe polynucleotide).

Fischer also teaches the added benefit that the primer allows selective amplification of members of a gene family (column 2, lines 55-60).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising amplification as taught by Mirkin et al in view of Pinkel et al and Weiss et al with the primers as taught by Fischer with a reasonable expectation of success. The modification would result in using primers having the tags therein (i.e., claim 7), a polyadenlyated tail of mRNA (i.e., claim 8), and primers that bind to a plurality of different sequences (i.e., claim 9). The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing selective amplification of members of a gene family as explicitly taught by Fischer (column 2, lines 55-60).

11. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) and further in view of Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) and Fischer (U.S. Patent No. 5,876,932, issued 2 March 1999) as applied to claim 9 above, and further in view of Caetano-Anolles (U.S. Patent No. 5,962,221, issued 5 October 1999).

Regarding claim 10, the method of claim 9 is discussed above in Section 10. While Fischer teaches degenerate primers (column 3, lines 25-39), neither Mirkin et al, Pinkel et al, Weiss et al, nor Fischer teaches the four 3′ residues are degenerate.

However, Caetano-Anolles teaches primers (i.e., SSR primers) having degenerate 3′ ends of 4 residues (e.g., 2 to 10 nucleotides in length) with the added advantage of allowing detection of polymorphisms (column 3, lines 22-31). The instantly claimed 4 bases is an obvious variant the 2-10 nucleotides as taught by Caetano-Anolles.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising amplification with degenerate primers as taught by Mirkin et al, Pinkel et al, Weiss et al and Fischer with the 3′ degenerate primers as taught by Caetano-Anolles with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing detection of polymorphisms as explicitly taught by Caetano-Anolles (column 3, lines 22-31).

12. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) and Fischer (U.S. Patent No. 5,876,932, issued 2 March 1999) as applied to claim 9 above, and further in view Kambara et al (U.S. Patent No. 5,985,556, issued 16 November 1999).

Regarding claim 11, the method of claim 9 is discussed above in Section 10.

While Fischer teaches primers comprising bases that bind more than one base (e.g., inosine, column 3, lines 25-39), neither Mirkin et al, Pinkel et al, Weiss et al, nor Fischer teaches bases at the four 3′ residues are degenerate.

However, Kambara et al teach a method of detecting a first probe in a first sample (e.g., sequencing a DNA fragment; Abstract) comprising a primer having inosine at the fourth position of the 3′

end of a primer with the added advantage of enhancing selectivity (column 31, lines 15-30). The instantly claimed "bases at the four 3' residues," which is broadly interpreted as being more than one base of the four 3' bases, is therefore an obvious variant of the one inosine at the fourth position as taught by Kambara et al.

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising amplification with degenerate primers as taught by Mirkin et al, Pinkel et al, Weiss et al, and Fischer with the bases that can base pair with more that one different base in the four 3' residues as taught by Kambara et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a primer having inosine at the fourth position of the 3' end of a primer with the added advantage of enhancing selectivity as explicitly taught by Kambara et al (column 31, lines 15-30).

13. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) as applied to claim 1 above, and further in view of Hunkapiller et al (U.S. Patent No. 5,942,609, issued 24 August 1999).

Regarding claim 12, the method of claim 1 is discussed above in Section 8.

Mirkin et al, Pinkel et al, and Weiss et al do not teach ligation.

However, Hunkapiller et al teach a method of detection of poly-nucleotides on solid supports (Title) comprising the ligation of polynucleotide sequences into oligonucleotides (column 3, line 50-column 4, line 33) with the added advantage that ligation (i.e., using DNA ligase) provides a proof-reading advantage that produces the correct ligation product (column 5, lines 21-25).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Mirkin et al in view of Pinkel et al and Weiss et al with the incorporation a sequence using a ligation as taught by Hunkapiller et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a proof-reading advantage that produces the correct ligation product as explicitly taught by Hunkapiller et al (column 5, lines 21-25).

14. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) as applied to claim 1 above, and further in view of Agrawal et al (U.S. Patent No. 5,652,103, issued 29 July 1997).

Regarding claim 13, the method of claim 1 is discussed above in Section 8.

Mirkin et al, Pinkel et al, and Weiss et al do not teach terminal transferase.

However, Agrawal et al teach a method of detecting a first probe in a first sample (e.g., determining nucleotide sequences; Abstract) wherein poly-nucleotides sequences are incorporated into oligonucleotides using terminal transferase with the added benefit that terminal transferase provides an efficient and reliable method for producing a molecule of suitable length for sequencing (column 3, lines 8-15).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Mirkin et al in view of Pinkel et al and Weiss et al with the incorporation a sequence using terminal transferase as taught by Agrawal et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in providing an efficient and reliable

method for producing a molecule of suitable length for sequencing as explicitly taught by Agrawal et al (column 3, lines 8-15).

15. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) as applied to claim 1 above, and further in view of Cleuziat et al (U.S. Patent No. 5,849,547, issued 15 December 1998).

Regarding claim 13, the method of claim 1 is discussed above in Section 8.

While Mirkin et al also teach the first probe comprises a base which is not selected from the group consisting of adenine, guanine, cytosine, thymine, and uracil (e.g., the linking oligonucleotide contains modified bases; page 23, lines 14-24), neither Mirkin et al, Pinkel et al, nor Weiss et al specifically teach the tag sequence comprises a base other that A,G,T,C, and U (i.e., hybridization of a probe to the modified base).

However, Cleuziat et al teach a method of detecting nucleic acids (e.g., amplifying target nucleic acids; Abstract) comprising hybridization to sequences containing modified bases with the added advantage that the resulting duplex exhibits greater stability (column 23, lines 29-34).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising hybridization of the first tag sequence as taught by Mirkin et al in view of Pinkel et al and Weiss et al with hybridization to bases other that A, G, C, T, and U as taught by Cleuziat et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in the resulting duplex exhibiting greater stability as explicitly taught by Cleuziat et al (column 23, lines 29-34).

16. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) as applied to claim 1 above, and further in view of Klinger et al (U.S. Patent No. 5,693,783, issued 2 December 1997).

Regarding claim 20, the method of claim 1 is discussed above in Section 8.

While Mirkin et al also teach the detection of probes in high molecular weight DNA (page 24, lines 18-23), Mirkin et al, Pinkel et al , and Weiss et al are silent with respect to metaphase chromosomes.

However, Klinger et al teach hybridization of probes to metaphase spreads of chromosomes (column 4, lines 23-27) with the added benefit of diagnosing chromosomal aneuploidies (column 2, lines 60-63).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Mirkin et al in view of Pinkel et al and Weiss et al with the metaphase chromosome spread as taught by Klinger et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in diagnosing chromosomal aneuploidies as explicitly taught by Klinger et al (column 2, lines 60-63).

17. Claims 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) as applied to claim 1 above, and further in view of Lebo (U.S. Patent No. 5,665,540, issued 9 September 1997).

Regarding claim 21, the method of claim 1 is discussed above in Section 8.

While Mirkin et al also teach the detection of probes in high molecular weight DNA (page 24, lines 18-23), Mirkin et al, Pinkel et al, and Weiss et al are silent with respect to interphase nuclei.

However, Lebo teaches the hybridization of probes to interphase nuclei with the added advantage of allowing the counting of adjacent gene copies and detection gene deletion (column 4, lines 38-50).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method as taught by Mirkin et al in view of Pinkel et al and Weiss et al with the interphase nuclei as taught by Lebo with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing the counting of adjacent gene copies and detection gene deletion as explicitly taught by Lebo (column 4, lines 38-50).m

Regarding claim 22, the method of claim 1 is discussed above in Section 5.

While Mirkin et al also teach the method wherein the target is a polynucleotide is located in a tissue (page 24, lines 18-20), Mirkin et al, Pinkel et al, and Weiss et al are silent with respect to fixed tissues.

However, Lebo teaches the hybridization of probes to cells that have been fixed (e.g., column 16, Example I) with the added advantage that fixing cells to slides minimizes false negative results (column 3, lines 17- 22).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method of detection in cells as taught by Mirkin et al in view of Pinkel et al and Weiss et al with the fixed cells as taught by Lebo with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in minimization of false negative results as explicitly taught by Lebo (column 3, lines 17-22).

18. Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mirkin et al (PCT International Publication No. WO 98/04740, published 5 February 1998) in view of Pinkel et al (U.S. Patent No. 5,690,894, issued 25 November 1997) Weiss et al (U.S. Patent No. 5,990,479, issued 23 November 1999) as applied to claim 1 above, and further in view of Kohne (U.S. Patent No. 5,612,183, issued 18 March 1997).

Regarding claim 29, the method of claim 1 is discussed above in Section 8.

Mirkin et al, Pinkel et al, and Weiss et al are silent with respect to determining the amount of the probe present in the sample.

However, Kohne teaches a method of hybridizing nucleic acids that determines the amount of probe in a sample (i.e., a method of determining the degree of and quantitating nucleic acid hybridization, Abstract) with the added advantage that the quantitation allows detection of the sensitivity of organisms to antimicrobial agents (column 12, lines 17-33).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the method comprising the detection as taught by Mirkin et al in view of Pinkel et al and Weiss et al with determining the amount of probe present as taught by Kohne with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing detection of the sensitivity of organisms to antimicrobial agents as explicitly taught by Kohne (column 12, lines 17-33).

Conclusion

19. No claim is allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

21. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER

Robert T. Crow
Examiner
Art Unit 1634